Ferrocenylalkylation processes under electrospray ionization conditions

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The electrospray ionization behavior of some ferrocenylalkylazoles $CpFeC_5H_4CH(R)Az$ (AzH are derivatives of imidazole, pyrazole, triazole and their benzo analogs; R = H, Me, Et, Ph), ferrocenylalkanols $CpFeC_5H_4CH(R)OH$ (R = H, Me), and mixtures of the latter with azoles was studied. The electrospray ionization mass spectra of these compounds, in addition to the molecular ion $[M]^{+\bullet}$, the protonated molecule $[M + H]^+$, and ferrocenylalkyl cation $[FcCHR]^+$ peaks, exhibit also intensive peaks for the binuclear ions $[(FcCHR)_2X]^+$ (X = Az or O), resulting from ferrocenylalkylation of the initial compounds with the ferrocenylalkyl cations. Electrospray ionization of an equimolar mixture of ferrocenylmethanol $FcCH_2OH$ and imidazole gives the protonated ferrocenylmethylimidazole molecule $[FcCH_2Im + H]^+$ and the $[FcCH_2(Im)_2 + H]^+$ dimer, apart from the ions typical of each component, *i.e.*, ferrocenylalkylation of azoles with the ferrocenylalkylcarbinols, known in the chemistry of solutions, takes place under electrospray conditions.

Key words: ferrocene, azoles, mass spectrometry, reactivity, electrospray ionization, ferrocenylalkylation.

The relatively new electrospray ionization (ESI) mass spectrometry technique is widely used to analyze ionic and highly polar compounds, most often, biomolecules,[1,2] which are able to dissociate and add protons or metal cations in polar solvents to give ionic products. Studies of low-polarity neutral compounds by this method are much more rare. This is due to the fact that the mechanism of formation of ions from these compounds is still debated.[3] Among the variety of mechanisms under discussion, the mechanism considering an ESI ion source as a flow-type electrochemical cell where ions are formed upon redox processes appears to be the most substantiated.[4,5] It was shown that ferrocene and some of its simple derivatives are easily oxidized under ESI conditions to give ferricinium cations, which are responsible for intensive peaks in the ESI mass spectra.[6—10] Therefore, it was proposed to use the ferrocenyl group as an electrochemical label for modification of, for example, alcohols, phenols, and carbohydrates[11—13] to analyze them by ESI.

In the present work, we studied the ESI reactivity of some biologically active ferrocenylalkylazoles (FAA)[14,15] given by the formula $CpFeC_5H_4CH(R)Az$ (AzH is imidazole, 2-methylimidazole, 3,5-dimethylpyrazole, 2,3-dimethylindole, indazole, benzimidazole, benzotriazole and their derivatives; R = H, Me, Et, Ph), ferrocenylalkylamines $CpFeC_5H_4CH(R)Am$ (AmH is dimethylamine, piperidine; R = H, Me), and ferrocenylalkanols $CpFeC_5H_4CH(R)OH$ (R = H, Me) (Scheme 1).

Results and Discussion

The ESI mass spectra of all compounds **1—14** exhibit analytically significant peaks for the molecular ion $[M]^{+\bullet}$, $[M + H]^+$, and for the ferrocenylalkyl cation $[FcCHR]^+$ (A) resulting from the carbon—heterocycle bond cleavage. Meanwhile, together with this set of ions, which reflect the composition and the structure of the compounds under study, peaks of ions with molecular weights greater than that of the molecular ion peak are also present and have a high (often the highest) intensity. This refers to the protonated dimer ions $[M_2 + H]^+$ **1**, **4**, **8**, **9**, **11—14**, which formally correspond to the reaction between protonated and neutral ferrocenylalkylazole molecules, and to the binuclear $[(FcCHR)_2Az]^+$ ion formed upon alkylation of the initial molecule with the ferrocenylalkyl cation (see Scheme 1, Table 1). The mass spectrum of compound **8** containing the set of characteristic ions is presented in Fig. 1. Note that a similar charged binuclear product is usually formed in the acid-catalyzed reaction of azoles with excess ferrocenylcarbinols.[16] Ferrocenylalkylation of diazoles and triazoles involves a different nitrogen atom.

Apparently, bisferrocenylalkyl ions derived from imidazole **4** and **12**, 2-methylimidazole **8**, **11**, and **13**, 3,5-dimethylpyrazole **5**, and their benzo analogs **1**, **3**, **7**, **9**, and **14** are formed by a similar path under ESI conditions. However, the binuclear ion peaks occur also in the spec-

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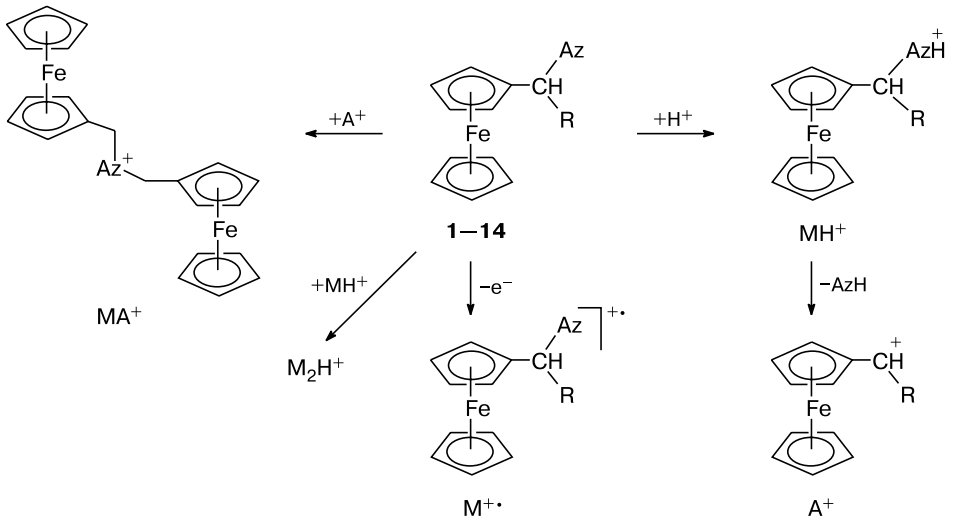
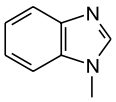
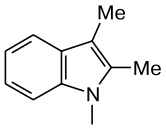
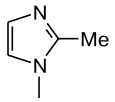
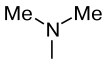
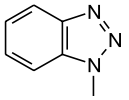
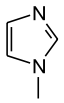
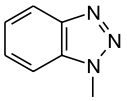
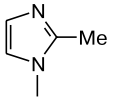
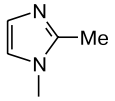
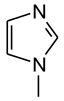
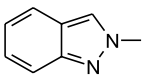
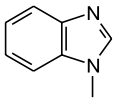
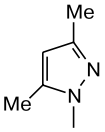
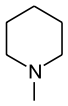
Scheme 1



Compound	R	Az	Compound	R	Az	Compound	R	Az
1	H		**6**	H		**11**	Et	
2	H		**7**	Me		**12**	Et	
3	H		**8**	Me		**13**	Ph	
4	H		**9**	Me		**14**	Ph	
5	H		**10**	Me				

tra of the ferrocenylalkyl derivatives of the dimethylindole **6**, piperidine **10**, and dimethylamine **2**, containing only one nitrogen atom (see Table 1). For compounds **6** and **10**, ferrocenylalkylation is accompanied by elimination of a hydrogen atom, *i.e.*, alkylation can occur at one of carbon atoms. In the case of ferrocenylmethyldimethylamine **2**, the ferrocenylalkyl cation adds apparently to the nitrogen atom to give the corresponding ammonium cation $(FcCHR)_2NMe_2^+$.

Thus, upon electrospray ionization, FAA undergo ferrocenylalkylation to give binuclear ions. This suggests that classical ferrocenylalkylation of azoles with ferrocenylcarbinols can also take place under these conditions. To verify this assumption, we studied the ESI mass spectra of some ferrocenic alcohols and azoles and their equimolar mixtures.

The spectra of ferrocenylalkanols FcCH(R)OH (R = H, Me) contain molecular ion peaks $[M]^{+\bullet}$, corresponding to ferrocenylalkyl cations $[FcCHR]^+$, as well as bi- and trinuclear products $[(FcCHR)_nO]^{+\bullet}$ ($n = 2, 3$), which are formed upon ferrocenylalkylation of the initial alcohol (Fig. 2). It is noteworthy that ferrocenylalkyl ethers are readily formed from the corresponding alcohols in acidic media[17] and are formed as by-prod-

Table 1. Relative ion peak intensities in the ESI mass spectra of compounds (the designations of ions are given in Scheme 1)

Compound	I_{rel} (%)						
	A	M	MH	MA	MA-1	M_2	M_2H
1	3.4	5.3	3.5	86.3	0.0	0.1	1.4
2	15.2	19.1	61.8	3.8	0.0	0.0	0.0
3	23.8	54.6	3.3	2.9	11.2	4.3	0.0
4	3.2	12.5	18.3	45.8	0.0	0.0	20.1
5	8.2	2.5	1.0	88.3	0.0	0.0	0.0
6	5.9	13.9	0.0	10.6	69.6	0.0	0.0
7	18.3	1.9	0.1	79.7	0.0	0.0	0.0
8	8.6	0.1	25.5	58.5	6.0	0.7	0.6
9	4.3	89.3	0.0	4.5	1.2	0.0	0.7
10	20.9	4.0	70.0	2.7	2.4	0.0	0.0
11	7.7	0.0	22.7	68.4	0.0	0.0	1.2
12	14.7	17.7	12.7	29.9	0.0	0.0	25.0
13	7.5	3.1	34.9	45.4	2.2	0.0	6.9
14	6.9	0.4	12.8	63.5	0.0	2.1	14.3

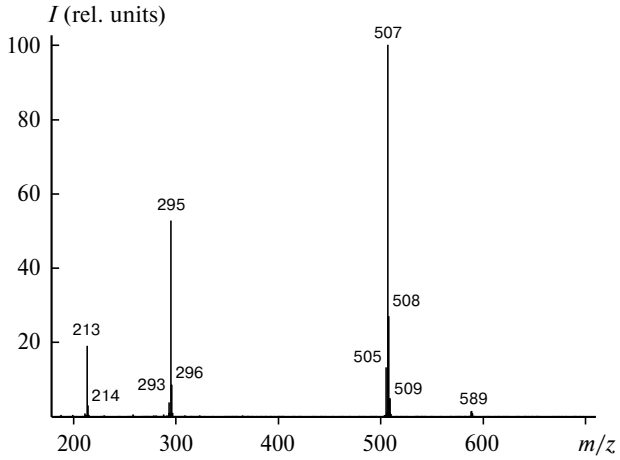


Fig. 1. ESI mass spectrum of compound **8**; *m/z*: 213 ($[FcCHMe]^+$), 294 ($[M]^{+\bullet}$), 295 ($[M + H]^+$), 507 ($[(FcCHMe)_2Az]^+$), 589 ($[M_2 + H]^+$).

ucts of ferrocenylalkylation of azoles with ferrocenylcarbinols.

Azoles are protonated under electrospray conditions to give protonated molecules $[M + H]^+$, protonated dimers $[M_2 + H]^+$ and $[M_3 + H]^+$, and their doubly charged ions $[M_3^{2+} + H]$ (Fig. 3).

On combined spraying of an equimolar mixture of ferrocenylmethanol $FcCH_2OH$ and imidazole (ImH), the protonated molecule $[FcCH_2Im + H]^+$ (*m/z* 267) and $[FcCH_2Im + ImH]^+$ (*m/z* 335) are formed in addition to those considered above, which are typical of each component of the mixture (see Fig. 4). The appearance of these ions indicates that ferrocenylalkylation of azoles with ferrocenylalkylcarbinols takes place under electrospray conditions.

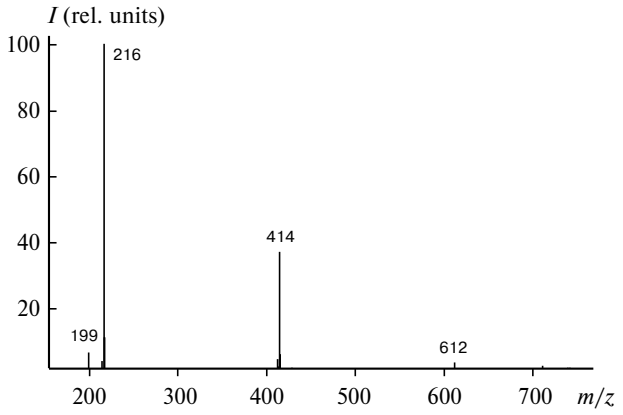


Fig. 2. ESI mass spectrum of $FcCH_2OH$ (in MeCN, $C = 3 \cdot 10^{-4}$ mol L^{-1}); *m/z*: 199 ($[FcCH_2]^+$), 216 ($[M]^{+\bullet}$), 414 ($[(FcCH_2)_2O]^{+\bullet}$), 612 ($[(FcCH_2)_3O]^+$).

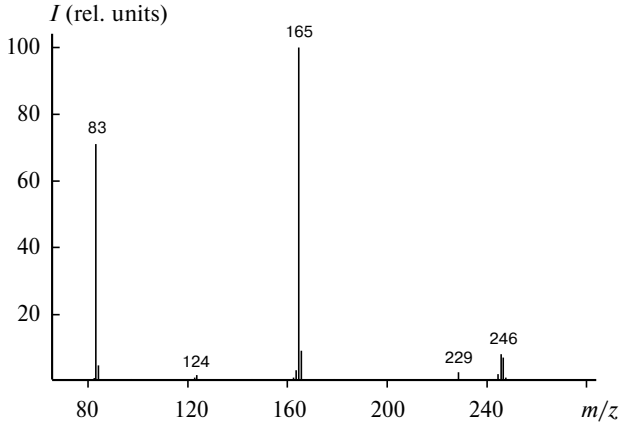


Fig. 3. ESI mass spectrum of 2-methylimidazole (in MeCN, $C = 3 \cdot 10^{-4}$ mol L^{-1}); *m/z*: 83 ($[M + H]^+$), 124 ($[M_3^{2+} + H]$), 165 ($[M_2 + H]^+$), 247 ($[M_3 + H]^+$).

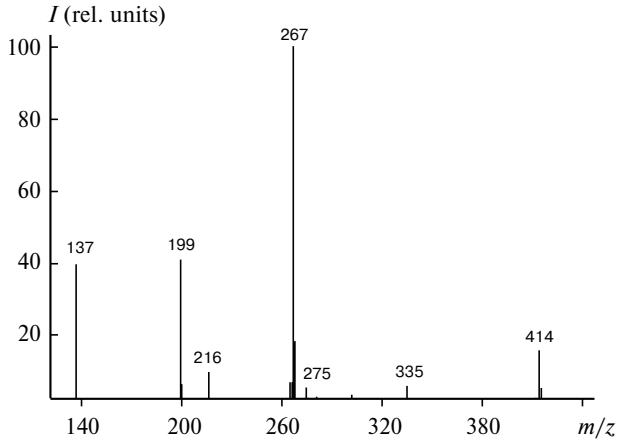


Fig. 4. ESI mass spectrum of an equimolar mixture of $FcCH_2OH$ and imidazole (in MeCN, $C = 3 \cdot 10^{-4}$ mol L^{-1}); reaction products: $[FcCH_2\ ImH]^+$ (*m/z* 267), $[FcCH_2ImH + ImH]^+$ (*m/z* 335).

Thus, it was shown for the first time that electrospray ionization of FAA, ferrocenylalkylamines, ferrocenylalkanols, and mixtures of the latter with azoles is accompanied by ferrocenylalkylation reactions well-known in the chemistry of solutions, giving charged products with mass numbers greater than those of the molecular ions of the initial compounds. This essentially restricts the analytical scope of electrospray ionization as applied to neutral ferrocene derivatives. However, the analogies we found between the processes occurring in solutions and during the ESI allow one to use this method to study the reactivity of ferrocene derivatives in the boundary zone between the liquid and gas phases.

Experimental

Compounds **1—4**, **6**, **9**, **10**, **12**, **14** (see Ref. 18) and **5**, **7**, **8**, **11**, **13** (see Ref. 19) were synthesized by known procedures. Ferrocenylalkanols were prepared as described previously.[20] All compounds were characterized by elemental analysis, ^{1}H NMR spectroscopy, and EI mass spectrometery. The structures of compounds **1** and **4** (see Ref. 21) and **6** (see Ref. 19) were confirmed by X-ray diffraction.

ESI mass spectra were recorded on a Finnigan LCQ Advantage tandem instrument with an octapole ion trap (temperature of the heated capillary 90 °C, electrical potential 4.5 kV, mass range 50—2000 Da) and an XCalibur 1.3 automatic data collection program.

Solutions of samples (5 μL) in MeCN were injected at a flow rate of the mobile phase equal to 50 μL min^{-1}. The spectra were converted to the monoisotopic form by the AELITA program.[22]

Previously, we noted that the peak intensities of FAA under electron ionization[23] depend on the nature of the heterocyclic fragment (its ionization energy) and under ESI conditions depend substantially on experimental parameters[24] (analyte concentration, heated capillary temperature, electrical potential, flow rate of the mobile phase, and the nature of the solvent). Therefore, the spectra of all compounds were recorded under the same conditions at a concentration of $3 \cdot 10^{-4}$ mol L^{-1}. The ESI spectra of mixtures of ferrocenylmethanol with imidazole were measured at an electrical potential of 6—8 kV, because at lower values the $[FcCH_2ImH]^+$ peak intensity was not more than 5% of I_{max}.

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